

Prevalence and impact of SARS-CoV-2 viral respiratory co-infections on disease severity in children and adults

A Review

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ABSTRACT

Introduction: The burden of SARS-CoV-2 has been widely recognized. However, it is not yet fully known whether a co-infection with another viral respiratory pathogen influences disease severity, mortality and length of hospital stay. Therefore, this paper aims to gather information on the impact of SARS-CoV-2 on disease severity and mortality, while also having a co-infection in both, children and adults.

Methods: We searched PubMed, Embase, Medline, PLOS Journals, Wiley Online Library and bioRxiv, to retrieve all relevant English papers. Studies that assessed the co-infection between SARS-CoV-2 and another respiratory pathogen and additionally also reported on disease severity, hospitalization or mortality were included.

Results: Ultimately, 22 studies have been included in this review. In total 1593 (5%) cases of co-infection have been reported among 32,383 patients. We identified ten different respiratory pathogens that caused co-infection. The mortality rate among co-infected patients was 9% and the reported time of hospitalization varied between 6.9-20 days.

Conclusion: In conclusion, our analysis showed conflicting results regarding the co-infection and its effect on disease severity. The presence of co-infection showed increased risk of severe illness, mortality and hospitalization in some studies and in other studies we did not observe that. The findings in this study support the need for diagnostic testing to identify and treat patients with SARS-CoV-2 co-infection.

Keywords: respiratory co-infections, SARS-CoV-2 severity, SARS-CoV-2 infection, SARS-CoV-2 variants of concern

LAYMEN SUMMARY

COVID-19 pandemic has caused a lot of burden worldwide in hospitals, as well as in daily life. Symptoms of the infection with SARS-CoV-2 can range from no symptoms to critical illness, during which people can also die. There are some risk factors which may contribute to the development of the more severe or critical illness when infected with SARS-CoV-2. One of those risk factors could possibly also be a co-infection between SARS-CoV-2 and another respiratory pathogen. Previously identified pathogens included respiratory syncytial virus, common human coronaviruses, rhinovirus, influenza A/B and parainfluenza viruses types 1–4. And as the co-infection can cause changes to the structure of the virus and the way it is transmitted; it can also mean that it may alter the disease severity in case of a co-infection. So, the aim of this review is to identify the spread and impact of co-infections between SARS-CoV-2 and another pathogen. This pandemic has left a lot of consequences on every aspect of life, especially on the healthcare systems. Therefore, it is important to understand what happens during the co-infection, so that the hospitals can better manage treatment and more efficiently use equipment and medication.

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel beta-coronavirus and in total, the seventh coronavirus currently known that infects humans [1, 2, 3]. This coronavirus was discovered in Wuhan, China at the end of 2019 and by March 2020 it has already spread all around the world [1, 3]. Similarly, as with all viruses, SARS-CoV-2 is constantly changing through mutation and many different sets of the mutation have been observed worldwide. All of these mutations could cause the virus to have higher transmissibility, disease severity and ability to evade vaccine-induced and natural immunity [5]. WHO has classified the SARS-CoV-2 mutations into three different categories: variants of concern (VOC), variants of interest (VOI) and variants under monitoring (VUM). A VOI is a SARS-CoV-2 variant that is predicted or known to affect virus characteristics such as transmissibility, disease severity, and immune escape. Additionally, it is identified to cause significant community transmission or multiple COVID-19 clusters in various countries and is an emerging risk to global public health. As of April 2022, there are no known circulating VOIs, however 8 VOIs were circulating in the past – Epsilon, Zeta, Eta, Theta, Iota, Kappa, Lambda and Mu. A variant becomes a VOC if it meets the definition of a VOI and in addition also shows an increase in transmissibility or a significant change in COVID-19 epidemiology as well as an increase in virulence and a decrease in the effectiveness of public health. Since the beginning of the pandemic, there are 5 known VOCs – Alpha, Beta, Gamma, Delta and Omicron. Delta and Omicron are the current circulating VOCs [6] (Figure 1). Each of these variants has caused slightly different symptoms, but in general the most frequently reported symptoms of SARS-CoV-2 infection are loss of taste or smell, fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, sore throat, congestion or runny nose, nausea or vomiting and diarrhea [7, 8].

Figure 1. Sars-CoV-2 variants of concern [4].

Variants of concern				
				
May 2020 UK	August 2020 South Africa	November 2020 Brazil	October 2020 India	November 2021 Multiple countries
Spreads more easily	Spreads more easily and some vaccines may be less effective against it	Spreads more easily and some vaccines may be less effective against it	Spreads more easily Symptoms may present differently May reduce vaccine efficacy Still protects against severe disease	Early studies show that it spreads more easily

The severity of the symptoms and the risk of hospitalizations among children and adults

As previously mentioned, the patients infected with SARS-CoV-2 can experience a variety of symptoms and these can range from no symptoms to critical illness. Generally speaking, the criteria for the SARS-CoV-2 infection can be grouped into the following categories [9, 10]:

- **Asymptomatic or Presymptomatic Infection:** This category includes individuals, who have tested positive for SARS-CoV-2 on the virologic test (antigen test or nucleic acid amplification test – NAAT), however they show no symptoms that are consistent with COVID-19. The percentage of patients with this type of infection is variable and not completely defined. Currently it is completely known how many asymptomatic patients later progress to clinical disease [9, 10]. A study by Zhang et al. (2020) reported that some asymptomatic individuals showed to have objective radiographic findings, that are consistent with COVID-19 pneumonia [11].
- **Mild Illness:** Individuals who exhibit any of the following symptoms i.e., fever, headache, loss of smell and taste, cough, sore throat, nausea, malaise, muscle pain, vomiting, diarrhea; but

who do not experience shortness of breath, dyspnea or abnormal chest imaging. Around 40% of people infected with SARS-CoV-2 experience mild disease and they can be managed through telephone calls or in an ambulatory setting [9]. The imaging or specific laboratory evaluations are not performed. Older patients or patients with comorbidities have a higher chance of progression of the disease into a moderate or severe illness, so those patients must be closely monitored [10].

- **Moderate Illness:** The individuals who belong to this category show evidence of lower respiratory disease during clinical assessment or imaging and who have oxygen saturation (SpO_2) $\geq 94\%$ on room air at sea level. Patients with moderate illness should be closely monitored as the pulmonary disease can quickly progress to a more severe illness [10]. Approximately 40% of people infected with SARS-CoV-2 experience moderate illness [9].
- **Severe Illness:** Individuals who have $\text{SpO}_2 < 90\%$ on room air at sea level, lung infiltrates $> 50\%$, a respiratory rate > 30 breaths/minute or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PAaO}_2/\text{FiO}_2$) < 300 mm Hg [10]. Approximately 15% of patients experience severe illness and most of them require oxygen support [9].
- **Critical Illness:** This category includes individuals who have respiratory failure, multiple organ dysfunction and/or septic shock. In addition to the pulmonary disease, the patients may also experience renal, cardiac, hepatic, central nervous system or thrombotic disease. 5% of patients infected with SARS-CoV-2 experience critical illness [9, 11].

The severity of the symptoms and the risk of developing a critical illness depend on certain risk factors, but also the SARS-CoV-2 variant type. The risk factors associated with a more critical illness and consequently also hospitalization include age (more than 60 years old), male sex, obesity, hypertension, asthma, chronic kidney disease, arrhythmia and metabolic syndrome [12]. The majority of people who died of COVID-19 were older than 65 years old and the odds of death in patients with less than 60 years have been estimated to be 18.8 times higher than those of younger patients.

Throughout the pandemic there have been reports of deaths from COVID-19 even in the younger population and in general, from the start of the pandemic there has been an increase in all-cause mortality among young adults [13]. The study by Tripathi et al. (2021) showed that among 152 young adults (18-40 years old) who were infected with COVID-19, nearly 25% of the patients experienced critical illness, 12.5% required invasive ventilation and 3.2% died during the hospitalization. As mentioned previously, different SARS-CoV-2 strains also have different rates of hospitalization. The study by Twohig et al. (2022) compared the levels of hospitalizations among patients infected with either the alpha or delta strain of SARS-CoV-2. They found that patients infected with the delta variant had more than two times the risk of being hospitalized when compared to patients infected with the alpha strain [14]. The risk factors among the young people included presence of any comorbidities, male sex and obesity. Children and adolescents experience milder diseases and more favorable outcomes than adults, however, some children also experience a critical disease and even death. The risk factors for developing severe illness in infants and young children include heart disease, asthma, seizure disorders, prematurity in young infants, chronic lung disease, obesity and immunocompromised status [15]. The group of Choi et al. (2022) did a systematic review on morbidities related to the severity of COVID-19 in young children and found that neonates had a high risk of experiencing severe COVID-19 illness. Additionally, a study by Martin et al. (2022) reported a 6.1% hospitalization rate among children and a median age of 11.9 years [16]. These numbers are similar to previously reported studies, where the hospitalization rates were 9.9% and 12%, respectively [17, 18].

Trends in other viral respiratory viruses during COVID-19

Measures, such as cessation of global travel, mask use, physical distancing and staying at home were intended to slow down the spread of COVID-19. Consequently, all of these measures also reduced the transmission of other viral respiratory pathogens. CDC reports decreased levels of influenza activity in March 2020, with record low numbers through the summer of 2020. The low numbers continued from

October 2020 to May 2021. Circulation of other respiratory pathogens during COVID-19 pandemic - respiratory syncytial virus (RSV), common human coronaviruses (HCoVs) types OC43, NL63, 229E, and HKU1, and parainfluenza viruses (PIVs) types 1–4 have also decreased [19]. A study by Oh et al. (2021) done in Germany and a study by Wan et al. (2021) done in Singapore have both reported a decrease in the circulation of respiratory viruses. The study of Oh et al. (2021) does mention that certain confounding factors need to be considered, for example at the beginning of the pandemic the general population did not seek as much medical care, which can potentially result in low reported numbers of viral infections. However, the reports of other viral illnesses remained low even when the majority of restrictions have been lifted and mobility levels have returned to normal, therefore the fact that people did not seek medical care does not appear to be the primary cause for a drop in notifications. After the restrictions were lifted, only rhinovirus reappeared at the pre-pandemic levels and these findings were supported by studies done in various countries around the world [21, 22, 23, 24].

Co-infections during SARS-CoV-2 infection

Patients who experience SARS-CoV-2 infection can at the same time also experience a different kind of infection. A few previous studies estimated that the prevalence of respiratory co-infections among adults is around 3% [25, 26, 27]. The most common respiratory co-infections that have been reported in the previous studies are rhinoviruses, adenoviruses and other coronaviruses. Additionally, a smaller percentage of people also had a combined, SARS-CoV-2 and Influenza infection. Contrary to influenza viruses, adenoviruses and rhinoviruses have been already in the past – before SARS-CoV-2; more commonly reported to be involved in various viral co-infections [27]. Respiratory viral co-infections during SARS-CoV-2 infection can be problematic as they can lead to viral interference. Viral interference can cause one virus to limit or suppress the replication of the second virus or to enhance the disease severity as compared to infection with only one virus [28].

As previously mentioned, children infected with SARS-CoV-2 experience less severe COVID-19 symptoms, however the percentage of viral co-infections among children have been estimated to be

higher than among adults. Wu et al. (2020) reported that 51% of children infected with SARS-CoV-2 showed viral co-infection with another pathogen while a study by Li et al. (2021) showed 33,5% of children infected with SARS-CoV-2 also experienced another respiratory co-infection.

This review aims to identify the prevalence and impact of co-infections between SARS-CoV-2 and another pathogen. This pandemic has left a lot of consequences on every aspect of life, especially on the healthcare systems. Therefore, it is important to understand what happens during the co-infection, so that the hospitals can better manage treatment and more efficiently use equipment and medication.

OBJECTIVE

The primary objective of this review paper is to assess the prevalence of SARS-CoV-2 viral respiratory co-infections in different settings (community, primary and hospital care) and assess the impact of SARS-CoV-2 co-infections on disease severity/burden in both children and adults.

METHODS

Search strategy

The literature search was performed using international databases PubMed, Embase, Medline, PLOS Journals, Willey Online Library and bioRxiv, to retrieve all relevant English papers. The search strategy used combined the following search terms: (COVID-19 OR SARS-CoV-2) AND (disease severity) AND (respiratory co-infections OR viral co-infections OR viral coinfection OR coinfect* OR co-infect* OR secondary infect* OR concomitant infect* OR mixed infect) AND (adult OR child). The search strategy for PubMed included the following search terms: (COVID-19[MeSH Terms]) AND (disease severity[MeSH Terms]) AND (respiratory co-infections OR viral co-infections[MeSH Terms]) OR

coinfections OR coinfection*) AND (adult[MeSH Terms] OR child[MeSH Terms]). Included studies were done between January 2020 and February 2021. Additionally, some papers were found through the manual checks of the article references.

Study selection

All studies are written in the English language, that came up during the search have been screened for inclusion in the systematic review. Inclusion criteria were a) prospective or retrospective cohort design, b) respiratory viral co-infections with SARS-CoV-2 and another viral pathogen, c) disease severity after co-infection, d) reported patient status after co-infection – ICU/non-ICU, ventilation used/not used, death, length of hospital stay. Additional criteria we looked for, that were not mandatory were the reports of SARS-CoV-2 viral strain and its effect on the co-infection and consequently also disease severity. Exclusion criteria included case studies, no reports on co-infection, no reports on disease severity after co-infection, editorials, reviews, qualitative studies, articles where the full texts were not available, non-peer-reviewed preprints, and studies combining other respiratory pathogens – bacterial and fungal infection. The first screening was done by reading through the abstract, titles and the objectives of the studies, to see if they met the inclusion criteria. This was followed by the second, full-text reading. Data of the eligible studies were then extracted into a common extraction template. For each study we extracted the following: first author name, study setting, country of the study, data collection period, the total number of patients, number of infected patients, age group of patients, gender, type of respiratory co-infection, percentage of patients that were accepted to ICU, percentage of patients that were ventilated, percentage of the infected patients who died, disease severity and risk of bias.

Outcome measures

The primary outcome measure of this study was to assess the prevalence of SARS-CoV-2 viral respiratory co-infections in different settings, such as community, primary and hospital care and consequently evaluate the disease severity of the patients. The disease severity can be estimated as an asymptomatic, mild illness, moderate illness, severe illness and critical illness. Additionally, we looked into how long the patients stayed at the hospital, if they had to go to the ICU, if they were ventilated, and how many patients with co-infections died.

Risk of bias assessment

The risk of bias was assessed for each study in this review. We used the online tool [31] to estimate the bias in the included studies. The assessment was done based on four domains: selection, ascertainment, causality and reporting. These domains estimated if participants in the study are representative of the entire population if exposure and outcome were adequately assessed, if there are potentially any other explanations for the outcome to occur (if the follow-up period was long enough) and lastly, if the study described participants insufficient details, to allow for replication of the study. Based on the results, we estimated the studies as low, medium or high risk.

Analysis

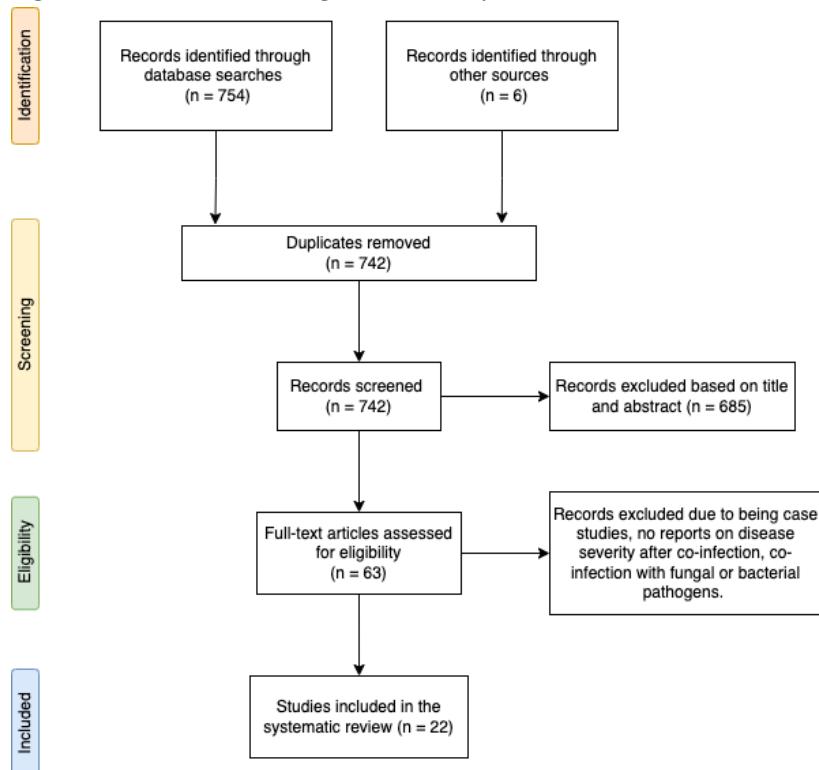
This systematic review aims to review the existing literature based on our objectives. The primary outcome was to assess the prevalence of respiratory viral co-infections with SARS-CoV-2 and another viral pathogen. Our aim was also to see if the co-infection leads to more severe disease illness and/or hospitalization among infected adults and children. We anticipated high levels of heterogeneity, considering the studies were done in different countries and the countries have different policies in testing and managing SARS-CoV-2.

RESULTS

Search results

Initially after the search through the databases (PubMed, Embase, Medline, PLOS Journals, Willey Online Library and bioRxiv) 754 papers were identified that matched our search strategy. Additionally, six articles were found through other sources. After the removal of duplicate papers, our search retrieved 742 articles, of which 685 were removed in the initial screen based on the title and abstract. The abstracts, titles and objectives of the 63 remaining studies have been screened in detail. A further 41 studies have been excluded as they failed to meet our inclusion criteria. The most frequent reasons for exclusion of the studies during the full-text reading stage were the case studies and respiratory infections with bacterial or fungal pathogens, where the results about severity were mixed and therefore, we could not determine whether the type of the infection affects the disease severity. 22 studies met our inclusion criteria and have therefore been included in the systematic review. The PRISMA flow diagram for the current analysis is depicted in figure 2.

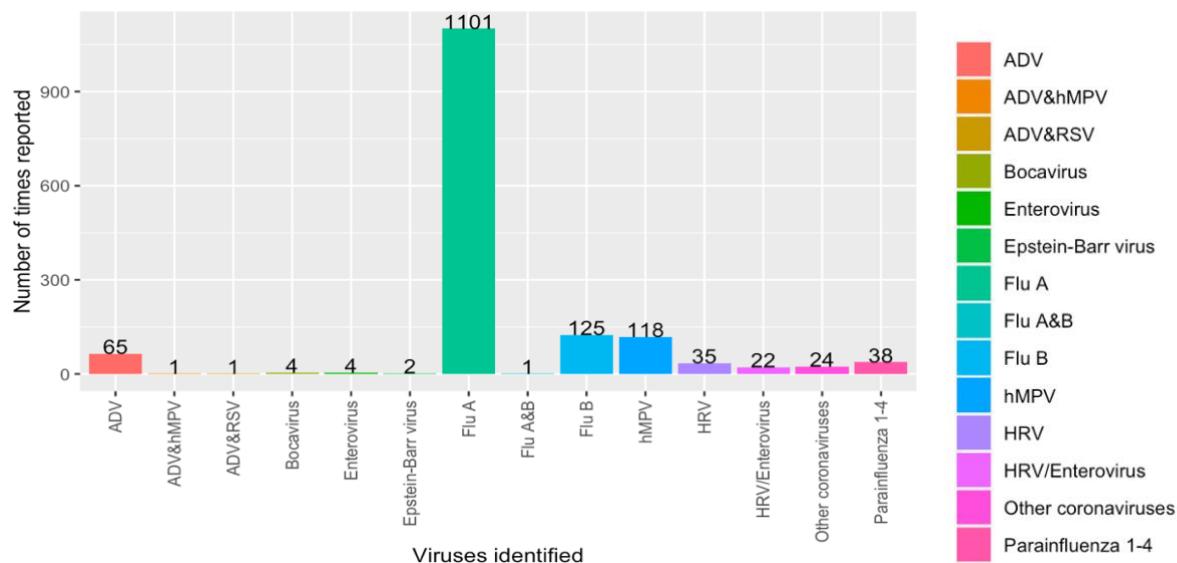
Figure 2. PRISMA flow diagram for study selection



Study characteristics

This literature review included 22 studies, among which were four prospective cohort studies, fifteen retrospective cohort studies, two matched case-control designs, and one cross-sectional design. Study characteristics are shown in Table 1. The studies were performed in various countries with the majority from China (32%), followed by the US (14%) and Brazil (9%). Other countries, with one study each (4.5%) were France, Singapore, Japan, Iran, Italy, Spain, South Korea, Saudi Arabia, England, and Canada. The study setting of the majority of the studies was the hospital/health care center. Studies included either only children (3, 14%), only adults (9, 41%), or a mix of children and adults (9, 41%). One study [32] did not specifically mention the age group of the population included. Studies included the patients who were either hospitalized or not hospitalized. A total of 32,383 patients were included across all studies, among which there were 1,593 (5%) reports on the co-infection between SARS-CoV-2 and another pathogen. The pathogens reported in the studies included adenovirus, human metapneumovirus, bocavirus, respiratory syncytial virus, enterovirus, Epstein-Barr virus, influenza A, influenza B, rhinovirus, other coronaviruses, and parainfluenza 1-4.

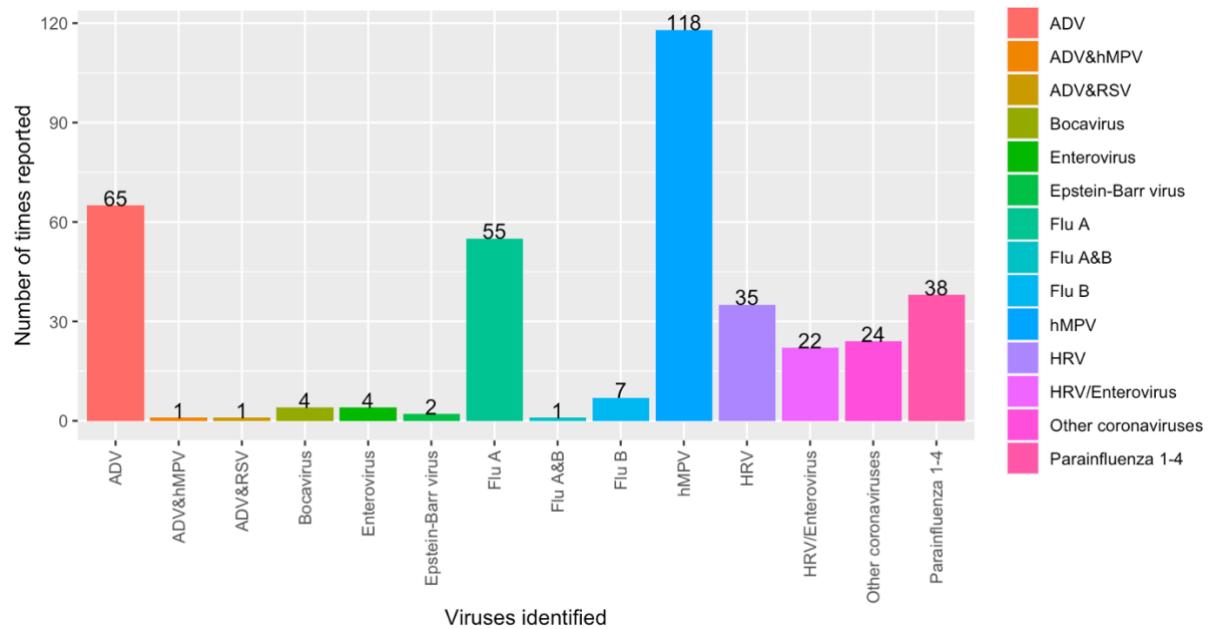
Figure 3. The viruses identified in the combination with co-infection with SARS-CoV-2 across all studies



Types of co-infections

All of the studies included in the current analysis reported a respiratory viral co-infection between SARS-CoV-2 and another pathogen, with most studies looking into various respiratory pathogens. Six studies [40, 41, 47, 48, 50, 51] were specifically focusing on the detection of the Influenza co-infection among SARS-CoV-2 infected patients. Additionally, the study of Alvares et al. (2021) only looked into the co-infection of SARS-CoV-2 and human rhinovirus. The overall prevalence of co-infections among people infected with SARS-CoV-2 was 5%. The most frequently reported pathogen that caused a co-infection was influenza A with 1101 cases combined across all studies. 1046 (95%) of those cases were reported in studies that only looked into influenza [40, 41, 47, 48, 50, 51]. Similarly, 118 (94.4%) out of 125 cases of influenza B were reported in the influenza-only studies. Therefore, we will discuss those studies separately as they are not representative of the actual situation regarding co-infections. The prevalence of co-infections after exclusion of influenza-only studies from the overall analysis halved to 2.8%. Among the studies that looked into a variety of pathogens that caused co-infection reported 377 cases of co-infections. The most commonly reported co-infections were with human metapneumovirus (118, 32.3%) and adenovirus (65, 17.2%) cases. The other reported respiratory pathogens including influenza A (55, 14.6%), parainfluenza 1-4 (38, 10%), human rhinovirus (35, 9.3%), other coronaviruses (24, 6.4%), the enterovirus or human rhinovirus (22, 5.8%) – one study did not differentiate between the viruses, influenza B (7, 1.9%), enterovirus (4, 1.1%), bocavirus (4, 1.1%) and Epstein-Barr virus (2, 0.5%). There were also three reports about a triple infection with SARS-CoV-2 and the reported pathogens included adenovirus and human rhinovirus, adenovirus and human metapneumovirus, and lastly, between Influenza A and B. The representation of the pathogens derived from the studies is depicted in Figure 3. In Figure 4, we see the representation of the pathogens that caused co-infection when we exclude influenza-only studies.

Figure 4. The viruses were identified in the combination with co-infection with SARS-CoV-2 when we remove the data from influenza-only studies.



Co-infection and disease severity

Among the studies included in this review, eleven (50%) reported on the disease severity through a number of people who needed mechanical ventilation, % of patients who were at ICU and the before mentioned criteria for the SARS-CoV-2 infection (asymptomatic, mild illness, moderate illness, severe illness, critical illness) [9, 10, 11]. The co-infection and disease severity data among the co-infected people has been very heterogeneous. The majority of the studies included in the analysis did not find an association between the co-infection with SARS-CoV-2, another pathogen, and increased disease severity. Based on the analysis from different studies, only the studies which reported on influenza co-infection showed that the co-infection was more likely to develop into severe-type illness. The study by Yue et al. (2020) reported that patients co-infected with SARS-CoV-2 and influenza B virus were more likely to develop into severe-type illness compared with those coinfected with influenza A. However, two studies that also assessed the co-infection between SARS-CoV-2 and influenza found the opposite results. The study by Chekuri et al. (2021) even reported that patients with only SARS-COV-2 infection were more likely to be admitted to the hospital than patients with a co-infection.

Therefore, in the majority of the studies, the co-infected patients showed no significant differences when compared to patients with only SARS-CoV-2 infection, regarding the disease severity.

Co-infection and mortality

Thirteen (59%) of the included studies reported on mortality. There were a lot of conflicting results about the co-infection and disease severity. Similarly, as for the co-infection and disease severity, some studies reported a higher mortality when patients had co-infection with SARS-CoV-2 and influenza. One study [34] reported that patients infected with the co-infection had a non-statistically significant higher risk of dying compared to patients only infected with human rhinovirus. However, other studies that also looked into a variety of viruses involved in a co-infection reported the opposite results and stated that co-infection did not increase the probability of morbidity and mortality. In total fifteen studies reported on the mortality among patients with co-infections. Additionally, one study [39] was done postmortem.

Co-Infection and length of hospital stay

Five of the 22 studies (22.7%) included in this literature review also reported on the length of the hospital stay [37, 38, 42, 46, 51]. Similar to the disease severity and mortality, there are also conflicting results when looking into the length of hospital stay. Two studies [38, 51] reported longer median hospitalization time for patients with only SARS-CoV-2 infection, and two studies reported the opposite [37, 46]. A study by Chen et al. (2020) found no difference in the length of stay between patients with co-infection and patients infected only with SARS-CoV-2. The reported time for the length of stay in the hospital varied between 6.9-20 days. The length of the stay did not seem to depend on the type of co-infection.

Table 1. Study characteristics with primary and secondary results

Study	Study setting	Country	Data collection period	Total n. of patients	N. of co-infected patients (%)	Age group of patients	Gender (% male)	Type of respiratory co-infection (%)	ICU (%)	Patients who were ventilated (%)	Infected patients who died (%)	Length of hospital stay (days)	Risk of bias
Prospective cohort design													
Wee et al., 2020 [32]	Single hospital study	Singapore	5.2.2020-15.4.2020	2807	6 (0.2%)	Adults	NR	RSV, 3 (50%) Other coronaviruses, 1 (20%) Parainfluenza 1-4, 2 (30%) HRV, 11 (34.4%) hMPV, 7 (21.9%)	NR	NR	1 (0.02%)	NR	Medium
Hirotsu et al., 2020 [33]	Multi-center study	Japan	2.3.2020-20.4.2020	191	32 (16.7%)	NR	NR	Other coronaviruses, 8 (25%) ADV, 2 (6.3%) RSV, 2 (6.3%) ADV & RSV, 1 (3.1%) ADV & hMPV, 1 (3.1%) HRV, 62 (67%) ADV, 14 (15%) Flu A, 2 (2%) Flu B, 2 (2%)	NR	NR	NR	NR	Medium
Le Glass, et al., 2021 [34]	Laboratory	France	1.3.2020-28.2.2021	6034	93 (1.5%)	Children and adults	53.8%	Enterovirus, 4 (4%) hMPV, 3 (3%) Parainfluenza 1-4, 9 (10%) RSV, 1 (1%) Other coronaviruses, 6 (6%) Bocavirus, 3 (3%)	9 (15.5%)#	NR	4 (6.9%)*	NR	Low
Antunes Eisen et al., 2021 [35]	Multi-center study	Brazil	March 2020 – December 2020	987	51 (5.2%)	Children and adults	51.8%	Flu A, 6 (6%) ADV, 18 (19%) HRV, 27 (29%)	NR	NR	NR	NR	Low
Retrospective cohort design													
Roh et al., 2021 [36]	Healthcare center, hospital, quarantine offices	South Korea	9.2.2020-23.2.2020	342	18 (5.3%)	Children and adults	62.9%	Flu A, 3 (16.6%) RSV, 6 (33.3%) ADV, 2 (5.5%) hMPV, 1 (5.5%) HRV, 1 (5.5%) Other coronaviruses, 5 (27.8%)	NR	NR	NR	NR	Low
Chekuri et al., 2021 [37]	Single large multi hospital academic medical center study	USA	11.3.2020-11.4.2020	306	15 (5%)	Adults	52.3%	Parainfluenza virus 1-4, 2 (13.3%) ADV, 1 (6.7%) RSV B, 1 (6.7%)	6 (1.9%)	4 (1.3%)	0	6.9	Low

Alvares, 2021 [38]	Single hospital study	Brazil	1.3.2020-30.9.2020	32	6 (18.8%)	Children	59.3%	RSV, 6 (100%) hMPV, 3 (6.1%) Bocavirus, 9 (18.4%) ADV, 2 (4.1%) Parainfluenza 1-4, 4 (8.2%) RSV, 8 (16.4%) Flu A (H1N1), 18 (36.8%) Flu A (not subtyped), 5 (10.2%)	3 (9.3%)	1 (3%)	1 (3%)	7	Low
Hashemi et al., 2021 [39]	Multi-center study	Iran	2.3.2020-20.4.2020	1444	49 (3.4%)	Children and adults	NR	Flu A, 44 (95.7%) Flu B, 2 (4.3%) Parainfluenza 1-4, 4 (27%) RSV, 3 (20%) ADV, 3 (20%) Flu A, 2 (13%) Flu B, 3 (20%) RSV, 3 (30%) HRV, 3 (30%)	NR	NR	49 (100%)§	NR	Medium
Ma et al., 2020 [40]	Single hospital study	China	28.1.2020-29.2.2020	93	46 (49.5%)	Adults	54.8%	Flu A, 44 (95.7%) Flu B, 2 (4.3%)	NR	NR	22 (23%)	NR	Low
Cheng et al., 2020 [41]	Single hospital study	China	28.1.2020-23.3.2020	213	97 (45.5%)	Adults	50.2%	Flu A, 97 (45.5%) Parainfluenza 1-4, 4 (27%)	NR	2 (1%)	8 (4%)	NR	Low
Chen et al., 2020 [42]	Single hospital study	China	1.1.2020-10.2.2020	203	15 (7.4%)	Adults	53.2%	RSV, 3 (20%) ADV, 3 (20%) Flu A, 2 (13%) Flu B, 3 (20%) RSV, 3 (30%) HRV, 3 (30%)	NR	39 (19.2%)	2 (1%)	20	Low
Grazzino et al., 2020 [43]	Multi-hospital study	Italy	25.3.2020	168	10 (6%)	Children	55.9%	Epstein-Barr virus, 2 (20%) Flu A, 1 (10%) Other coronaviruses, 1 (10%)	2 (1.2%)	2 (1.2%)	0	NR	Low
Alosaimi et al., 2021 [44]	Single hospital study	Saudi Arabia	NR	48	34 (70.1%)	Children and adults	77%	Flu A (H1N1), 17 (50%) ADV, 10 (29%) Flu A, 1 (4.3%) RSV, 6 (26.1%)	14 (29%)	NR	9 (19%)	NR	
Kim et al., 2020 [24]	Laboratory	USA	3.3.2020-25.3.2020	115	23 (20%)	Children and adults	45%	Parainfluenza virus 1-4, 3 (13%) hMPV, 2 (8.7%) HRV, 8 (24.8%) Other coronaviruses, 5 (21.7%)	0	0	0	NR	Low
Tagarro et al., 2020 [45]	Multi hospital study	Spain	2.3.2020-16.3.2020	41	2 (4.9%)	Children	44%	Flu B, 2 (5%) RSV, 3 (27.3%)	9.7%	4 (10%)	0	NR	Low
Tang et al., 2021 [46]	Single hospital study	China	29.1.2020-15.2.2020	78	11 (14.1%)	Adults	52.6%	Flu B, 1 (9.1%) ADV, 1 (9.1%) +	2 (18.2%)	2 (18.2%)	NR	13	
Yue et al., 2020 [47]	Single center study	China	12.2.2020-21.2.2020	307	176 (57.3%)	Adults	47.3%	Flu A, 153 (86.9%) Flu B, 23 (13.1%)	NR	NR	NR	NR	Medium
Wu et al., 2020 [48]	Hospital	China	18.1.2020-26.4.2020	1386	726 (52.4%)	Adults	50.5%	Flu A, 659 (91%) Flu B, 67 (9%)	842 (61%)	842 (61%)	59 (8.1%)	NR	Low

Scott et al., 2021 [49]	Laboratory	USA	March 2020-February 2021	371	53 (14.3%)	Children and adults	48.1%	HRV/Enterovirus, 22 (41.51%) hMPV, 18 (33.9%) ADV, 12 (22.6%) Bocavirus, 1 (1.9%)	NR	NR	NR	NR	Medium	
Matched case-control design														
Stowe et al., 2021 [50]	Multi-center study	England	20.1.2020-25.4.2020	16764	58 (0.3%)	Children and adults	NR	Flu A (not subtyped), 31 (53.4%) Flu A (H1N1), 8 (13.8%) Flu B, 16 (41.4%) Flu A & B, 1 (1.7%) Unknown Flu type, 2 (3.4%)	7 (12%)	7 (12%)	25 (43%)	NR	Low	
Yu et al., 2020 [51]	Single center study	China	28.1.2020-18.2.2020	128	64 (50%)	Adults	43%	Flu A, 54 (84.4%) Flu B, 10 (15.6%)	NR	NR	7 (10.9%)	17	Low	
Cross-sectional design														
Peci et al., 2021 [52]	Hospitals, clinics, assessment centers	Canada	11.1.2020-20.4.2020	325	8 (2.7%)	Children and adults	NR	HRV, 2 (25%) Other coronaviruses, 2 (25%) RSV, 2 (25%) hMPV, 2 (25%)	NR	NR	NR	NR	Low	

* hMPV = human metapneumovirus, RSV = respiratory syncytial virus, HRV = rhinovirus, ADV = adenovirus, Flu A = Influenza A, Flu B = influenza B, NR = not reported

Estimation only for patients co-infected with SARS-CoV-2 and RSV

+ Other infections were caused by the bacteria Mycoplasma pneumoniae

§ This study was done postmortem

DISCUSSION AND CONCLUSION

This current literature review investigated how and if the co-infection between SARS-CoV-2 and another viral respiratory pathogen affects the disease severity. Additionally, we looked into the prevalence of different co-infections and which co-infection was the most prevalent in the studies included in the review. In general, co-infection is thought to worsen the disease outcomes and it usually also leads to more severe symptoms. Additionally, co-infection can also modify the virulence of the virus and cell death. This would mean that it alters the disease severity [41]. Therefore, we wanted to analyze if this also happened in patients that were co-infected with SARS-CoV-2 and other respiratory viruses. The results of this review show that approximately 5% of the COVID-19 patients also experienced another, secondary infection and 9% of the patients with co-infection died. When looking into the prevalence of mortality, we excluded one study [39], as it was done postmortem.

The most commonly reported viral co-infection with SARS-CoV-2 was Influenza A and most of the reports on co-infections with influenza A happened in China. Cheng et al. (2020) reported that the data suggests that there was a high prevalence of Influenza A in China at the beginning of the pandemic as 45.5% of participants had a co-infection. The high prevalence of influenza A during the beginning of the COVID-19 pandemic is in line with expectations as COVID-19 started during winter and northern China (where most of the studies were based) follows a winter pattern in influenza prevalence [53]. Another reason for the high number of influenza co-infection cases in the current analysis is that four of the included studies looked specifically into the co-infection between SARS-CoV-2 and Influenza A and have therefore not taken any other viral co-infections into account. Considering six of the studies [40, 41, 47, 48, 50, 51] included in this review only looked into influenza co-infections, we decided to discuss those results separately. Additionally, studies done in other countries reported a low prevalence of influenza cases or co-infections [25, 32, 33].

Other viral co-infections that were found in both adults and children and included human metapneumovirus, adenovirus, human rhinovirus, parainfluenza 1-4 and other coronaviruses. All of these are common respiratory viruses that are a part of the standard testing panel for respiratory viruses. All of these viruses cause mild cold symptoms in healthy individuals [54]. The ratio of women to men was similar across all studies, which suggests that both genders have the same level of susceptibility to secondary infections. Only a study done by Hashemi et al. (2020) found a high prevalence of co-infections in older men. The results on the age of patients who experienced co-infection were showing opposite results. As mentioned, Hashemi et al. (2020) found a higher prevalence of co-infections in older males. Similarly, Alosaimi et al. (2021) reported that co-infection showed an increasing trend with age. On the other hand, Peci et al. (2021), Le Glass et al. (2021), and Chekuri et al. (2021) found that patients with co-infection were younger than patients with only SARS-CoV-2 infection. Additionally, Roh et al. (2021) reported that viral loads in patients infected with only SARS-CoV-2 did not significantly differ from patients with a respiratory co-infection. Scott et al. (2021) reported that children under 10 years old showed a higher co-infection rate than older children.

The current analysis showed a lot of conflicting results regarding disease severity. Yue et al. (2020) reported that patients with influenza B and SARS-CoV-2 co-infection were more likely to develop a severe-type illness and consequently a higher mortality rate. Wu et al. (2020) also looked into the prevalence of co-infections between SARS-CoV-2 and influenza and reported that people who were co-infected with influenza A were less likely to develop the severe disease ($OR = 0.514$, 95%CI: 0.360–0.732) and die ($OR = 0.671$, 95% CI: 0.463–0.973) than people with only SARS-CoV-2 infection. On the other hand, the group of people co-infected with influenza B showed no statistically significant difference in more severe disease or mortality when compares to only SARS-CoV-2 infection ($OR = 0.903$, 95% CI: 0.359–2.272). The study of Stowe et al. (2020) showed that patients with co-infection of influenza and SARS-CoV-2 were twice as likely to develop severe illness and die. Le Glass et al. (2021) looked into co-infection between SARS-CoV-2 and human rhinovirus and showed that the co-

detection of both viruses is associated with mild COVID-19. Additionally, they found a non-statistically significant increased risk of being transferred to an intensive care unit and dying in people with co-infection when compared to people with only HRV. Chekuri et al. (2021), Cheng et al. (2020), and Alvares et al. (2021) all report that there was no difference in patients with co-infection when compared to patients with a single infection regarding ventilation, need for intensive care or mortality. The only difference these studies show is the length of hospital stay, where Chekuri et al. (2021) reported a short hospital stay in co-infected patients and Alvares et al. (2021) reported a longer stay when patients had a co-infection. The reason behind this contradiction in the length of the hospital stay might be that Alvares et al. (2021) looked into the co-infection in children and Chekuri et al. (2021) looked into adults.

The contradictory results have been supported by other studies that looked into viral co-infections as some studies showed worsened clinical outcomes, while others showed no or even improved clinical outcomes. That suggests a highly complex mechanism that impacts the clinical outcomes during the co-infection [43]. Another factor that could influence the results is the presence of comorbidities. Some of the studies included in the analysis identified comorbidities, such as hypertension, diabetes, COPD, heart and lung disease. Some studies did not take this information into account and therefore the results might be biased. A lot of the studies included in the literature review were done at the beginning of the pandemic. That was the time when most of the people were still not wearing masks, were not socially distancing themselves from other people, and have not yet been vaccinated. That could be one of the reasons for the high numbers of influenza A cases in China. Additionally, as the pandemic progressed and people started wearing masks more often, the rate of respiratory viruses declined and there were not as many reports on the co-infections [19]. People were also less likely to visit their doctor or go to the hospital if they had only mild complaints.

The strengths of this review include the extensive search strategy, with specific inclusion and exclusion criteria. Additionally, this review combines the current knowledge about SARS-CoV-2 and other respiratory co-infections and its effect on disease severity and mortality.

There are several limitations in this literature review. Firstly, some of the studies included a low sample number, therefore it is hard to generalize the results. Secondly, as mentioned previously there was a lot of heterogeneity among the studies as they were done in different countries and each country had its own rules on SARS-CoV-2 testing and therefore also the detection of co-infections. Thirdly, some of our outcomes, such as disease severity and mortality were difficult to assess as there are not many studies who report on them, and the ones who do show contradictory results. Finally, most of the studies were done in the beginning of 2020 and a few of the studies only looked into the co-infection between SARS-CoV-2 and influenza. Therefore, the estimation of the co-infection shows overestimation of influenza co-infection cases.

The suggestion for the future research would be to look into how and if different SARS-CoV-2 strains affect respiratory viral co-infections and if they cause a higher or lower disease burden. It would also be interesting to repeat the studies in multiple different countries, where they would all test for the same respiratory viruses. That way we could get an overview on the prevalence of the respiratory viruses and the effect they have on the SARS-CoV-2 co-infection. Additionally, we could look into how the co-infections changed after the COVID-19 vaccine was introduced into society.

In conclusion, our analysis showed conflicting results regarding the co-infection and its effect on disease severity. We showed that 5% of the COVID-19 patients also experienced another, secondary infection and 9% of those patients died. The presence of co-infection showed increased risk of severe illness and mortality in some studies and in other studies we did not observe that. The findings in this study support the need for diagnostic testing to identify and treat patients with SARS-CoV-2 co-infection.

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